Ablation of persistent atrial fibrillation (AF) remains challenging, particularly as the duration of continuous AF before the procedure increases. Attainment of durable pulmonary vein (PV) isolation remains a fundamental goal in this population; continuous retriggering from focal peri-PV sources (both automaticity and localized reentry) as a potential mechanism for maintaining persistent AF was documented more than a decade ago. An area of continuing debate centers on the extent of additional atrial ablation outside the PV antra required for long-term maintenance of sinus rhythm. Two studies published in this issue of Circulation: Arrhythmia and Electrophysiology highlight important clinical aspects of this debate.

**Articles see p 287, 295, and 442**

Inoue and colleagues report long-term follow-up of catheter ablation in 263 patients with persistent AF (mean duration of continuous AF, 11 months; >1 year in 50%). To identify triggers that may perpetuate AF, cardioversion was performed at procedure onset, followed by short-duration isoproterenol infusion if needed, to provoke immediate recurrence of AF. The immediate recurrence of AF occurred in 70 (27%) of 263 patients, one third arising from non-PV foci. These triggers were then targeted for ablation (successful in all peri-PV foci, but in only 6 of 23 patients with non-PV triggers). All patients subsequently underwent PV isolation, and 72% had additional non-PV left atrial ablation. At the last follow-up of 17 months (38% of patients receiving antiarrhythmic drugs [AADs], multiple procedures in 30%, 90% of patients were in sinus rhythm, although 16% continued to have paroxysmal episodes. Immediate recurrence of AF was associated with a greater risk of recurrent persistent AF during follow-up, predominantly a result of inability to localize and eliminate non-PV focal triggers.

In a randomized trial of ablation for persistent AF, Dixit and coworkers evaluate 3 strategies for ablation of persistent AF: (1) PV isolation+ablation of non-PV triggers elicited by cardioversion and isoproterenol infusion (standard protocol), (2) standard protocol+empirical ablation at sites that commonly harbor non-PV foci (superior vena cava, crista terminalis, peri-coronary sinus os, and inferolateral mitral annulus), and (3) standard protocol+ablation of sites with complex fractionated electrograms as identified by automated algorithm (cycle length, <120 ms). Single-procedure efficacy (freedom from any atrial arrhythmias without AAD) was 49%, 58%, and 29% at 1 year in the 3 groups, respectively, and 53%, 62%, and 51% at final follow-up, respectively. The latter included repeat ablation using the standard protocol in 37% of patients. Additional AAD therapy in an unspecified number of patients, and a more lenient (but clinically reasonable) definition of rhythm control, led to efficacy rates of 64%, 70%, and 43% at 1 year and 80%, 82%, and 80% at the end of the study (mean, 19±9 months after last ablation), respectively. The first 2 strategies resulted in significantly better initial outcomes than ablation targeting electrogram fractionation. The authors conclude that additional substrate modification beyond PV isolation provides no improvement in single-procedure efficacy for patients with persistent AF.

Clinical trials comparing ablation approaches with careful delineation of techniques and outcomes, including the study of Dixit et al, are critical to evolution of optimal management strategies. However, there are several reasons for caution in generalizing from their conclusions. We do not know the duration of continuous AF before the procedure in the study population and, thus, the applicability of these data to patients with longer-duration persistent AF. Of the 55 patients randomized to the standard protocol alone, 8 (13%) had additional non-PV ablation for either induced macroreentrant atrial tachycardia or focal triggers at the initial procedure. The second strategy, involving the most extensive non-PV ablation (directed at potential trigger “hotspots”), demonstrated a nonsignificant trend toward the best outcome. In contrast to prior reports of improved initial outcomes with adjunctive electrogram-guided ablation, patients assigned to the third strategy actually had inferior outcomes in this study. As the authors point out, this finding could not be attributed to proarrhythmia (organized atrial tachycardias occurred with equal frequency across groups) and was more likely related to less complete PV isolation at the initial procedure. Data from repeat ablation point to the potential importance of PV triggering as a mechanism of recurrence; all patients had at least 1 PV reconnected, and 76% had evidence of reconnection in at least 3 PVs. However, >20% of patients in each group underwent additional left atrium ablation. Overall, up to one third of patients in the standard approach group received atrial ablation outside the peri-PV

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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**Editorial**

**Fibroblasts, Focal Triggers, and Persistent Atrial Fibrillation**

**Is There a Connection?**

David J. Wilber, MD
area for provoked or spontaneous triggers and tachycardias; it is unclear how the occurrence of such arrhythmias, and the ability to successfully eliminate them, influenced long-term outcome.

The results of PV isolation alone in the study of Dixit et al are not dissimilar to those reported by other investigators for patients with long-standing persistent AF, in whom freedom from recurrent atrial arrhythmias off AAD after either circumferential or antral isolation alone was 33% to 40% after a single procedure and 56% to 59% after multiple procedures.\(^4\)\(^6\) The conceptual model of trigger predominance early in the course of AF during paroxysmal episodes, with advancement to more persistent forms associated with progressive biatrial structural remodeling requiring more extensive (although relatively nonspecific) substrate ablation, is likely an oversimplification. Recent imaging studies demonstrate a broad overlap between AF clinical subtypes (paroxysmal, persistent, and long-standing persistent) and the extent of atrial substrate abnormalities reflected by delayed-advancement magnetic resonance imaging\(^7\)\(^8\) or echocardiographic integrated backscatter.\(^9\)

An issue raised by both Inoue et al\(^1\)\(^2\) and Dixit et al\(^3\) is how best to identify non-PV sites for ablation. Both studies attempted to elicit focal triggers by isoproterenol and cardioversion of spontaneous or induced AF at the start of the procedure. Yet, the reliability and reproducibility of these maneuvers for identifying triggers are poorly characterized. For the PVs, trigger induction is often inconsistent, with “arrhythmogenic” veins varying from one procedure to the next.\(^10\) This variability was one of several motivating factors in the movement from focal or targeted PV ablation to empirical encircling PV isolation. A similar issue involving the superior vena cava, one of the most common non-PV triggers,\(^11\)\(^12\) has led to some groups advocating routine isolation of this structure.\(^13\) The coronary sinus,\(^14\) left atrial appendage,\(^15\)\(^16\) and right atrium\(^17\)\(^18\) frequently harbor sites that drive persistent AF, but identification of these sources before ablation is challenging; their recognition as culprits is often delayed until ablation elsewhere has been completed. Finally, the stepwise approach to ablation of persistent AF is frequently associated with organized atrial tachycardias, as either transitional rhythms during the initial procedure or subsequent recurrences. Up to 50% of these rhythms are due to focal sources or localized reentry, rather than macroreentrant circuits.\(^19\)--\(^21\) Such rhythms may represent true proarhythmia arising directly from the impact of prior ablation lesions. Alternatively, they may reflect preexisting focal drivers uncovered after elimination of fibrillatory conduction.\(^22\) There is evidence that presentation with these arrhythmias after PV isolation, and their successful ablation, results in better long-term outcomes than presentation with continuing or recurrent AF alone.\(^21\)\(^23\)

Why is persistent AF associated with potentially more non-PV drivers? A third article in this issue of Circulation: Arrhythmia and Electrophysiology, an overview of the rapidly evolving field of myocyte-fibroblast interactions, provides additional perspective.\(^24\) Fibroblasts account for 50% to 70% of the total cells of the heart and play an important role in the integrated mechanical and electrical function of the atrium.\(^25\) In response to a variety of stimuli (hypoxia, mechanical stress, inflammation, and humoral factors), atrial fibroblasts proliferate and undergo differentiation to myofibroblasts. This is the cell type predominantly responsible for a broad range of secretory and signaling functions, as well as the production and turnover of extracellular matrix proteins (collagen, matrix metalloproteinases, and their inhibitors). The role of excess collagen deposition in the genesis of slowed conduction associated with AF has been well characterized.\(^26\) However, there is accumulating evidence for direct myocyte-fibroblast electrical coupling through heterocellular gap junctions and tunneling microtubules.\(^24\)\(^27\)--\(^30\) Although fibroblasts appear to lack the capacity for regenerative action potentials, their resting membrane potential is considerably less negative than that of myocytes. Depending on the extent and number of coupled fibroblasts, myocytes can be electrotonically depolarized to threshold (early afterdepolarization), resulting in increased ectopic beats and repetitive firing.\(^31\)\(^32\) Myofibroblasts may also electrotonically link isolated groups of myocytes, providing a mechanism for conduction (with significant delay) across fibrous barriers.\(^33\) At present, these interactions have been characterized predominantly in cell culture and through mathematical modeling; their role in intact atria and human AF is yet to be confirmed. Intriguing questions remain: is fibroblast proliferation and differentiation a regional process initiating and responsible for clinically demonstrated sites of non-PV drivers? Can this process or its consequences be imaged in vivo?

PV ectopic firing can drive AF in all forms of the disease, and its elimination plays an important role in controlling recurring and persistent episodes. Not unreasonable, this observation has led many investigators to focus predominantly on identifying technology and approaches that best produce durable PV isolation. However, alterations in the atrial substrate outside the PVs assume increasing importance in arrhythmogenesis during disease progression. Although atrial fibrosis and its impact on conduction has understandably received the most attention, it is a by-product of active processes (fibroblast proliferation and differentiation and myocyte-fibroblast coupling) that in themselves can lead to abnormal impulse formation and slowed conduction. An exciting prospect for the coming decade is that insights gleaned from the study of these complex interactions may better inform our selection of non-PV ablation targets and strategies.

Disclosures

None.

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